

(FILE 'HOME' ENTERED AT 12:28:53 ON 10 APR 2007)

FILE 'MEDLINE, EMBASE, CAPLUS' ENTERED AT 12:29:11 ON 10 APR 2007

L1 835 S (TLR OR (TOLL-LIKE)) AND (SYNERG? OR CRYSTAL?)
L2 197 S L1 AND PY<2004
L3 91 DUP REM L2 (106 DUPLICATES REMOVED)

FILE 'MEDLINE' ENTERED AT 12:45:26 ON 10 APR 2007

FILE 'MEDLINE, EMBASE, CAPLUS' ENTERED AT 12:54:02 ON 10 APR 2007

FILE 'MEDLINE' ENTERED AT 12:54:03 ON 10 APR 2007

FILE 'STNGUIDE' ENTERED AT 12:54:08 ON 10 APR 2007

=> d ti,au, so, ab 2,7,17,28,31,39

YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, CAPLUS' - CONTINUE? (Y)/N:y

L3 ANSWER 2 OF 91 CAPLUS COPYRIGHT 2007 ACS on STN
TI Immunostimulatory G,U-containing oligoribonucleotides, compositions, and screening methods
IN Lipford, Grayson; Bauer, Stefan
SO PCT Int. Appl., 220 pp.
CODEN: PIXXD2
AB Comps. and methods using immunostimulatory RNA oligomers are provided. The immunostimulatory RNA mols. are believed to represent natural ligands of one or more Toll-like receptors, including Toll-like receptor 7 and Toll-like receptor 8. The comps. and methods are useful for stimulating immune activation. Methods useful for screening candidate immunostimulatory compds. are also provided.

L3 ANSWER 7 OF 91 CAPLUS COPYRIGHT 2007 ACS on STN
TI The Interleukin 1 (IL-1) Receptor Accessory Protein Toll/IL-1 Receptor Domain: Analysis of putative interaction sites by in vitro mutagenesis and molecular modeling
AU Radons, Juergen; Dove, Stefan; Neumann, Detlef; Altmann, Reinhold; Botzki, Alexander; Martin, Michael U.; Falk, Werner
SO Journal of Biological Chemistry (2003), 278(49), 49145-49153
CODEN: JBCHA3; ISSN: 0021-9258
AB The Toll/interleukin 1 (IL-1) receptor family plays an important role in both innate and adaptive immunity. These receptors are characterized by a C-terminal homol. motif called the Toll/IL-1 receptor (TIR) domain. A principal function of the TIR domain is mediating homotypic protein-protein interactions in the signal transduction pathway. To suggest interaction sites of TIR domains in the IL-1 receptor complex, the authors modeled the putative three-dimensional structure of the TIR domain within the co-receptor chain, IL-1 receptor accessory protein. The model was based on homol. with the crystal structures of human TLR1 and TLR2. The final structure of the IL-1 receptor accessory protein TIR domain suggests the conserved regions box 1 and 2, including Pro-446, as well as box 3 within the C-terminal .alpha.-helix as possible protein-protein interaction sites due to their exposure and their electrostatic potential. Pro-446, corresponding to the Pro/His mutation in dominant neg. TLR4, is located in the third loop at the outmost edge of the TIR domain and does not play any structural role. Inhibition of IL-1 responsiveness seen after substitution of Pro-446 by charged amino acids is due to the loss of an interaction site for other TIR domains. Amino acids 527-534 as part of the loop close to the conserved box 3 are crit. for recruitment of myeloid differentiation factor 88 and to a lesser extent for IL-1 responsiveness. Modeling suggests that native folding of

the TIR domain may be approached by the responsive deletion mutants .DELTA.528-534 and .DELTA.527-533, whereas the C-terminal .beta.-strand and/or .alpha.-helix is displaced in the nonresponsive mutant .DELTA.527-534.

- L3 ANSWER 17 OF 91 MEDLINE on STN DUPLICATE 9
TI Synthetic vaccines: the role of adjuvants in immune targeting.
AU Jiang Zi-Hua; Koganty R Rao
SO Current medicinal chemistry, (2003 Aug) Vol. 10, No. 15, pp. 1423-39. Ref: 155
Journal code: 9440157. ISSN: 0929-8673.
- AB A clear understanding of the mechanism of function of immune stimulatory adjuvants, which commonly accompany vaccines, is beginning to emerge. Recent investigations have demonstrated that Toll-like receptors (TLRs) are the critical link between the innate and the adaptive immunity. This link, which is normally activated as a result of collaboration between adjuvants and TLRs in triggering adaptive immunity, has been a subject of several recent investigations. With the advent of well-defined synthetic small molecules, which are designed to either mimic the adjuvants or, as in many cases, to structurally represent pathogen associated molecular patterns, it is now possible to design reproducible experiments and to draw credible conclusions. An adjuvant alerts the host immune system through a mechanism similar to that of an infection by a pathogen, which involves interaction with a TLR followed by a 'danger signal' to the immune system. Secretion of cytokines and regulation of the expression of co-stimulatory molecules induced by innate response shape the magnitude and quality of adaptive response. Synthetic vaccines containing specific epitopes to which immune responses are desired, are expected to be far superior in target specificity while the benefits may be long-lasting. The immune responses by therapeutic vaccines are generally adaptive in nature and such responses often require the participation of the components of innate immunity, most importantly the TLRs and their pathogen-associated binding compliments. Structurally well-defined synthetic molecules derived from lipid A, muramyl di-peptide (MDP), and CpG motifs from bacterial DNA offer a wide range of immune stimulants for the development of fully synthetic vaccines. Lipo-peptide and self-adjuvanted antigens, in combination with additional immune stimulatory adjuvants in liposome delivery system, may be important in vaccine design. Combinations of synthetic mimics of microbial products are known to display synergistic effects in stimulating the immune system. Either alone or in combination with chemotherapy, innate immune therapy using TLR ligands to stimulate the immune system may offer an alternate therapeutic approach against rapidly mutating viral infections-(HIV/AIDS), and cancers.
- L3 ANSWER 28 OF 91 EMBASE COPYRIGHT (c) 2007 Elsevier B.V.. All rights reserved on STN
TI Leucine-rich repeats and pathogen recognition in Toll-like receptors.
AU Bell J.K.; Mullen G.E.D.; Leifer C.A.; Mazzoni A.; Davies D.R.; Segal D.M.
SO Trends in Immunology, (1 Oct 2003) Vol. 24, No. 10, pp. 528-533. .
Refs: 35
ISSN: 1471-4906 CODEN: TIRMAE
- AB Toll-like receptors (TLRs) are the major cell-surface initiators of inflammatory responses to pathogens. They bind a wide variety of pathogenic substances through their ectodomains (ECDs). Here, we ask: what is the structural basis for this interaction? Toll-like receptor ECDs comprise 19-25 tandem copies of a motif known as the leucine-rich repeat (LRR). No X-ray structure of a TLR -ECD is currently available but there are several high-resolution LRR-containing proteins that can be used to model TLRs. We suggest that the basic framework of TLRs is a horseshoe-shaped solenoid that contains an extensive .beta.-sheet on its concave surface, and numerous ligand-binding insertions. Together, these insertions and the

.beta.-sheet could provide a binding surface that is 10-fold greater in area than binding surfaces in antibodies and T-cell receptors.

- L3 ANSWER 31 OF 91 MEDLINE on STN DUPLICATE 20
TI Adenosine receptors and mammalian toll-like receptors:
synergism in macrophages.
AU Olah Mark E; Caldwell Charles C
SO Molecular interventions, (2003 Oct) Vol. 3, No. 7, pp. 370-4.
Ref: 44
Journal code: 101093789. ISSN: 1534-0384.
AB Adenosine is known to participate in tissue protection subsequent to ischemic events. New evidence points to a role for adenosine in promoting neovascularization through a mechanism that requires interaction with the Toll-like receptor (TLR) signaling pathway. In macrophages, the adenosine receptor subtype 2A (A(2A)R) synergizes with some but not all of the Toll-like receptors, leading to increased expression of vascular endothelial growth factor (VEGF). Simultaneously, the expression of tumor necrosis factor-alpha (TNFalpha) is decreased; this phenomenon depends on the presence of AR agonists; however, the activation of transcription factor nuclear factor-kappaB (NF-kappaB) is not attenuated in the presence of A(2A)R agonists. It appears that the addition of adenosine or other A(2A)R agonists can mediate the "angiogenic switch," in macrophages, from TNFalpha protein expression to expression of components necessary for angiogenesis. Although these observations might have important implications for wound healing, it will be important to discern whether this interaction between ARs and TLRs is necessary for angiogenesis associated with tumor growth.
- L3 ANSWER 39 OF 91 MEDLINE on STN DUPLICATE 22
TI Synergistic and antagonistic interactions between LPS and superantigens.
AU Dalpke Alexander H; Heeg Klaus
SO Journal of endotoxin research, (2003) Vol. 9, No. 1, pp. 51-4.
Journal code: 9433350. ISSN: 0968-0519.
AB Superantigens trigger polyclonal activation of T lymphocytes with cytokine release that eventually may lead to lethal cytokine syndrome (toxic shock). In contrast, bacterial components that are recognized by Toll-like receptors (e.g. LPS or CpG DNA) primarily target macrophages and dendritic cells. We have analyzed whether superantigens and TLR ligands interact with each other. We found that superantigens synergize with LPS in an IFN-gamma-dependent pathway. More important, we found compelling evidence that superantigens prime the innate immune cell system to a subsequent challenge with endotoxin. This sensitization was critically dependent on T-cell derived IFN-gamma. When we analyzed the underlying molecular mechanisms, we additionally found that TLR stimulation enhanced IFN-gamma-mediated cellular responses. Moreover, TLR ligands induced proteins of the SOCS family thus shutting off IFN-gamma-mediated cellular activation. Since IFN-gamma is synthesized by T cells after superantigen triggering, these results show that superantigen and TLR pathways are interconnected and regulate each other. They further show that the outcome of this interaction may include activation as well as down-regulation of the respective response pattern.

L3 ANSWER 53 OF 91 MEDLINE on STN DUPLICATE 33
 AN 2002489877 MEDLINE
 DN PubMed ID: 12244157
 TI Microbial recognition via Toll-like receptor-dependent
 and -independent pathways determines the cytokine response of murine
 dendritic cell subsets to CD40 triggering.
 AU Edwards Alexander D; Manickasingham Shivanthi P; Sporri Roman; Diebold
 Sandra S; Schulz Oliver; Sher Alan; Kaisho Tsuneyasu; Akira Shizuo; Reis e
 Sousa Caetano
 CS Immunobiology Laboratory, Cancer Research U.K., London Research Institute,
 London, United Kingdom.
 SO Journal of immunology (Baltimore, Md. : 1950), (2002 Oct 1) Vol.
 169, No. 7, pp. 3652-60.
 Journal code: 2985117R. ISSN: 0022-1767.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200211
 ED Entered STN: 28 Sep 2002
 Last Updated on STN: 30 Jan 2003
 Entered Medline: 12 Nov 2002

L3 ANSWER 71 OF 91 MEDLINE on STN DUPLICATE 45
 AN 2001544514 MEDLINE
 DN PubMed ID: 11592079
 TI Toll-like receptor expression reveals CpG DNA as a
 unique microbial stimulus for plasmacytoid dendritic cells which
 synergizes with CD40 ligand to induce high amounts of IL-12.
 AU Krug A; Towarowski A; Britsch S; Rothenfusser S; Hornung V; Bals R; Giese
 T; Engelmann H; Endres S; Krieg A M; Hartmann G
 CS Department of Internal Medicine and Division of Clinical Pharmacology,
 University of Munich, Munich, Germany.
 SO European journal of immunology, (2001 Oct) Vol. 31, No. 10, pp.
 3026-37.
 Journal code: 1273201. ISSN: 0014-2980.
 CY Germany: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 LA English
 FS Priority Journals
 EM 200112
 ED Entered STN: 10 Oct 2001
 Last Updated on STN: 22 Jan 2002
 Entered Medline: 4 Dec 2001

L3 ANSWER 16 OF 91 MEDLINE on STN DUPLICATE 8
 AN 2003253957 MEDLINE
 DN PubMed ID: 12778475
 TI CD40-dependent and -independent activation of human tonsil B cells by CpG
 oligodeoxynucleotides.
 AU Gantner Florian; Hermann Patrice; Nakashima Kosuke; Matsukawa Satoko;
 Sakai Katsuya; Bacon Kevin B
 CS Bayer Yakuhin, Ltd., Research Center Kyoto, Respiratory Diseases Research,
 Japan.. florian.gantner.fg@bayer.co.jp
 SO European journal of immunology, (2003 Jun) Vol. 33, No. 6, pp.
 1576-85.
 Journal code: 1273201. ISSN: 0014-2980.
 CY Germany: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals

EM 200307
ED Entered STN: 3 Jun 2003
Last Updated on STN: 1 Aug 2003
Entered Medline: 31 Jul 2003